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DOI: 10.1056/NEJMe2416323

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Middle Meningeal Artery Embolization and Nonacute Subdural Hematoma

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Nonacute subdural hematoma is common among older persons. With an aging population and increasing use of antiplatelet and anticoagulant agents, subdural hematoma is projected to become the most common cranial neurosurgical disease by 2030.¹ Standard treatments — including glucocorticoids and statins for milder cases, with the addition of surgery for more severe cases — are associated with a high risk of recurrence, which leads to repeat surgery in 15% of cases.^{2,3} Hematoma progression or recurrence is thought to arise from repeated hemorrhage from the outer vascularized hematoma membrane under the dura, which is supplied by the middle meningeal artery.

Embolization of the middle meningeal artery is thought to reduce the risk of hematoma progression and recurrence by addressing the source of hemorrhage. Preliminary evidence for middle meningeal artery embolization, most commonly performed with a liquid embolic agent of ethylene vinyl copolymer dissolved in dimethyl sulfoxide, suggests that it is safe and efficacious either as a stand-alone treatment or as an adjunct to surgery: the risk of recurrence resulting in rescue surgery is 5 to 10% and the risk of complications is less than 5% after embolization performed with or without surgery.^{4,5} There is also evidence that middle meningeal artery embolization is effective in special populations of patients who are

not surgical candidates, such as patients with coagulopathy.⁶

Three randomized, controlled trials published in the *Journal* evaluated the efficacy and safety of middle meningeal artery embolization plus standard treatment as compared with standard treatment alone among patients with nonacute subdural hematoma. Two of these trials — the Embolization of the Middle Meningeal Artery with Onyx Liquid Embolic System in the Treatment of Subacute and Chronic Subdural Hematoma (EMBOLISE) trial⁷ and the Managing Non-acute Subdural Hematoma Using Liquid Materials: a Chinese Randomized Trial of Middle Meningeal Artery Treatment (MAGIC-MT)⁸ — had a primary outcome related to recurrence or progression of subdural hematoma. In the EMBOLISE trial, standard treatment was surgical evacuation (burr-hole drainage or craniotomy, with burr-hole drainage being slightly more common), whereas in MAGIC-MT, 78% of the patients underwent burr-hole drainage (the only surgical treatment offered) and the remaining patients were treated medically. The EMBOLISE trial includes a cohort that did not undergo surgery, but the results for this cohort have not been presented.

The EMBOLISE trial showed a significant benefit of middle meningeal artery embolization plus surgery over surgery alone with regard to the risk of reoperation for recurrence or progression with-

in 90 days (4.1% vs. 11.3%). In MAGIC-MT, there was a smaller difference in the risk of recurrence or progression within 90 days between the embolization group and the usual-care group (−3.3 percentage points), and the result was not significant ($P=0.10$). The timing of adjunctive embolization may be one explanation for the difference in outcomes between these two trials. Middle meningeal artery embolization was performed before surgery in almost all the patients who received both interventions in MAGIC-MT, whereas embolization was performed after surgery in 42% of the patients who received both interventions in the EMBOLISE trial. The patient populations also differed in that all the patients in MAGIC-MT were Chinese and 22% of the patients who received usual care in MAGIC-MT did not undergo surgery.

The third trial — the Squid Trial for the Embolization of the Middle Meningeal Artery for the Treatment of Chronic Subdural Hematoma (STEM)⁹ — evaluated middle meningeal artery embolization plus standard treatment as compared with standard treatment alone with regard to a composite outcome assessed at 180 days (recurrent or residual hematoma; reoperation or surgical rescue; or major disabling stroke, myocardial infarction, or death from neurologic causes). Standard treatment consisted of either medical therapy or surgical evacuation performed with burr holes or a subdural evacuating port system. The trial showed an overall benefit of middle meningeal artery embolization: the risk of a composite-outcome event was 16% in the embolization group, as compared with 36% in the control group ($P=0.001$). In both STEM and MAGIC-MT, randomization was stratified according to whether surgery was indicated, and the percentage of participants who did not undergo surgery in STEM was larger than that in MAGIC-MT (39% vs. 22%). In these two trials, the benefit of middle meningeal artery embolization as an adjunct therapy seemed to derive largely from the subgroup of patients who did not undergo surgery, although this subgroup analysis was not part of a hierarchical statistical plan, so no direct inferences can be made.

With regard to safety, mortality at 90 days appeared to be higher in the treatment group than in the control group in the EMBOLISE trial

(5.1% vs. 3.0%, $P=0.32$), whereas in MAGIC-MT, serious adverse events (including death) occurred less frequently in the embolization group than in the usual-care group (6.7% vs. 11.6%, $P=0.02$). The reason for the differences between groups as well as the discrepancy between trials is unknown. In STEM, mortality at 180 days appeared to be higher in the embolization group than in the control group; of the 21 deaths recorded, 12 were in the embolization group (in 8% of the patients) and 9 in the control group (in 5%). It is important to note that in all three trials, the indication for rescue surgery after randomization was determined by the treating physician rather than by an independent committee, which could have been a source of bias.

In short, middle meningeal artery embolization as an adjunct to standard treatment for symptomatic nonacute subdural hematoma appears to have added benefit over standard treatment in preventing recurrence and progression, but further data are needed to define the true magnitude of the effect and to identify the cohort (those undergoing surgery or those receiving medical management) in whom such adjunct therapy is most effective. It is important to emphasize that middle meningeal artery embolization is not currently indicated as a replacement for surgical therapy for severely symptomatic patients in whom emergency surgical evacuation is indicated or for patients who are asymptomatic. Middle meningeal artery embolization is also not indicated for patients with acute subdural hematoma.

Other questions remain regarding the potential role of middle meningeal artery embolization in the management of subdural hematoma. These include whether the intervention can be used as a primary, stand-alone treatment in patients in whom urgent decompression is not indicated; whether the embolization material, such as particles and coils, matters; whether proximal or distal embolization matters; whether its safety is affected by the type of anesthesia (general or monitored anesthesia care); and how its effects may differ in special patient populations, such as patients in whom urgent resumption of anticoagulant or antithrombotic agents is indicated.

The EMBOLISE trial, MAGIC-MT, and STEM represent important coordinated efforts to study

middle meningeal artery embolization as an adjunct to standard treatment in patients with non-acute subdural hematoma. Further randomized, controlled trials with rigorous methods are needed to advance this burgeoning field.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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This editorial was published on November 20, 2024, at NEJM.org.

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DOI: 10.1056/NEJMe2410915

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Oral Infigratinib in Children with Achondroplasia — Targeted Treatment

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Thanks to advances in both basic and clinical research, the past 20 years have seen new awareness regarding the diagnosis, treatment, and unmet needs of persons with rare genetic disorders. Most inherited bone disorders are among such rare conditions.

Achondroplasia, the most common skeletal dysplasia, is characterized by disproportionate short stature with relatively short limbs, trident hands, midface hypoplasia, and foramen magnum stenosis. The disease-causing gene, identified in 1994 by Le Merrer,^{1,2} is now known to arise from heterozygous mutations in the gene encoding fibroblast growth factor receptor 3 (FGFR3) on chromosome 4p16.3. Additional molecular analyses have shown that FGFR3 is a negative regulator of chondrocyte proliferation and differentiation in the growth plate.³ FGFR3 variants in persons with achondroplasia result in excessive activation of the FGFR3 protein and, consequently, increased intracellular signaling,

which leads to the inhibition of chondrocyte assembling and proliferation in the growth plates.

Genetic insights have led to targeted treatment in achondroplasia. Several growth-promoting approaches (e.g., recombinant human growth hormone) were assessed without satisfying results.⁴ Vosoritide — a recombinant analogue of C-type natriuretic peptide (CNP) that is administered subcutaneously — addresses part of the altered intracellular chondrocyte signaling in achondroplasia and increases linear growth.^{5,6} In 2021, vosoritide was approved by the Food and Drug Administration and the European Medicines Agency for pediatric patients with genetically confirmed achondroplasia and open epiphyses.

In this issue of the *Journal*, Savarirayan and colleagues present the results of a phase 2 trial (PROPEL2) involving 72 children with achondroplasia between the ages of 3 and 11 years to evaluate the safety and efficacy of infigratinib, an orally bioavailable FGFR1–3 selective tyrosine